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Title: Acute aerobic exercise and neuroplasticity of the motor cortex: a systematic review.

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Abstract

Objectives. To synthesise the existing literature investigating if acute aerobic exercise enhances the response to experimentally-induced neuroplasticity paradigms.

Methods. A systematic search of electronic databases Medline, PsycInfo and Embase was undertaken on 26 April 2018 and updated on 17 May 2019. Studies were included if they involved a bout of aerobic exercise; prescribed a bout of rest as a control condition; utilized a non-invasive brain stimulation paradigm to induce neuroplasticity; used TMS to assess neuroplasticity outcomes; participants were healthy 18-65 year old males and females with no diagnosed neurological/psychological impairment.

Results. Eight papers (containing 12 experiments) met inclusion criteria. All studies utilized cycling or treadmill exercise as their exercise modality, and exercise intensity ranged from low intensity continuous exercise to high-intensity interval exercise. Four neuroplasticity paradigms were employed including paired associative stimulation (PAS) (n=3), continuous theta-burst stimulation (cTBS) (n=2), intermittent theta-burst stimulation (iTBS) (n=2) and transcranial direct current stimulation (n=1). Aerobic exercise enhanced neuroplastic responses (compared to rest) in seven of the 12 experiments.

Conclusions. This review provides emerging evidence that acute aerobic exercise can enhance the response to experimentally-induced TMS neuroplasticity paradigms. However, there remains great variability in the study design and reporting of effects in these studies and thus a more standardized approach is encouraged to better understand the relationship between acute aerobic exercise and neuroplasticity. Future studies should consider optimizing intensity, paradigms and duration of both exercise and neuroplasticity paradigms employed.

Key words: brain stimulation; neuronal plasticity; acute exercise

Introduction

Engaging in regular aerobic exercise enhances executive function, attention, memory and cognitive control [1-3]. Whilst these benefits have been reported across a variety of settings with diverse populations and using different exercise protocols, the underlying mechanisms of the relationships are still not fully understood. A number of mechanistic candidates have been suggested to underpin the relationship between aerobic exercise and cognitive performance; one of these is *via* the upregulation of neurotrophic factors such as brain-derived neurotrophic factor (BDNF), cortisol and lactate [4-6]. Indeed, evidence from both animal and human studies suggest BDNF promotes and modulates *neuroplasticity,* broadly understood as the brains capacity to undergo functional or morphological changes in response to experience. It is plausible that exercise induced changes in neuroplasticity also underlie changes in cognition [7, 8].

At the synaptic level, neuroplasticity is defined as an increase or decrease in the strength of synaptic connections between neurons in the brain in response to experience [9]. The mechanisms which underlie these changes in synaptic connections are classified as long-term potentiation (LTP) or long-term depression (LTD). LTP results in the prolonged strengthening of synaptic transmission between neurons due to repetitive coordinated activation; conversely, LTD drives a reduction in synaptic transmission between neurons due to the lack of coordinated activation [10]. Both LTP and LTD have been demonstrated in a number of synaptic populations in the mammalian brain during the formation of new memories, suggesting that these functions of neuroplasticity may underlie learning and memory [11].

The neuroplasticity of the human motor cortex can be measured using a safe and painless non-invasive brain stimulation technique called transcranial magnetic stimulation (TMS) [12]. When applied as single or paired-pulses, TMS can be used to measure changes in brain excitability in response to an intervention. Additionally, TMS pulses applied in rapid succession (trains) can induce changes in excitability, and thus induce neuroplasticity. There are many established TMS paradigms that either increase or decrease excitability within the cortex underlying the stimulated area. For example, repetitive transcranial magnetic stimulation (rTMS) paradigms such as intermittent theta-burst

stimulation (iTBS) and other paradigms delivered at high frequencies generally produce local increases in cortical excitability [13] and mechanisms are thought to be similar to LTP-like mechanisms commonly observed in animal models [14]. Alternatively, TMS paradigms including continuous theta-burst stimulation (cTBS) and other low frequency repetitive paradigms generally produce the opposite effect, resulting in a decrease in cortical excitability, with mechanisms proposed to be similar to LTD-like effects [15]. Additionally, paired associative stimulation (PAS), which involves precisely timing a peripheral electrical stimulus with TMS, and transcranial direct current stimulation (tDCS), which delivers a weak electrical current between two electrodes, can either produce LTP-like or LTD-like effects depending on the relative timing between the stimulations, and for tDCS, the electrode montages [16-18].

Studies in animal models provide evidence that non-invasive brain stimulation paradigms induce neuroplastic changes at the synaptic level [19, 20]. For example. LTD-like rTMS paradigms in rats have shown direct effects on the neuroplasticity of GABAergic (inhibitory neurotransmitter) synapses, and reduced expression of calcium-binding proteins expressed by inhibitory interneurons [19]. Similarly, an increase in hippocampal BDNF levels (thought to reflect synaptic-level changes in neuroplasticity) has been reported following application of a high-frequency rTMS paradigm in awake rats [20]. Taken together, these animal studies provide evidence that non-invasive brain stimulation paradigms alone have the capacity to induce neuroplastic changes at the synaptic level.

In addition to inducing neuroplasticity, TMS can also be used to measure neuroplastic changes. If TMS pulses of sufficient intensity are delivered to the primary motor cortex, the response to stimulation may be assessed in the peripheral muscle of interest by measuring the peak-to-peak amplitude of the motor-evoked potentials (MEPs) using surface electromyography (EMG) [12]. Comparing the changes in MEPs before and after the application of these neuroplasticity paradigms is an indicative measure of motor cortical neuroplasticity [12].

A considerable benefit of these measurement tools is the ability to assess the influence of external factors on neuroplasticity, non-invasively in awake human participants. A large number of studies have investigated the variability of responses to TMS paradigms in populations experiencing

psychological or neurological conditions, however this variability is also observed in healthy populations due to factors such as age, sex, pharmacological influence, genetics, and exercise [7]. A more complete understanding of the effects of exercise on neuroplasticity is important for not only mechanistic understanding, but may also inform exercise prescription in term of intensity, duration and exercise type. Therefore, the aim of the present systematic review was to synthesise the existing research investigating the effect of a single session of aerobic exercise on non-invasive brain stimulation measures of neuroplasticity in healthy adults.

Method

This review was structured using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [21] and was registered on PROSPERO in November 2018 (registration number CRD42018115860). Articles were extracted from Medline, PsycINFO and EMBASE databases. Searches were conducted on the 26th April 2018 and further updated on 17th May 2019.

The inclusion criteria were generated using a Population, Intervention, Comparator and Outcome (PICO) framework; the population (P), was 18-65 year old males and females with no diagnosed neurological disorder or impairment; intervention (I), was an acute bout of aerobic exercise; comparator (C), was a rest condition (control); and the outcome (O), was a non-invasive brain stimulation measure of neuroplasticity, such as changes in MEPs from pre to post plasticity paradigm. Terms that related to the outcome (plasticity, TMS) and intervention (exercise) were used as keywords in the search. All studies included were published in English as no expertise were available to translate studies in other languages.

Studies collated through the systematic searches were exported to Endnote (X8). Duplicates were initially removed using the 'remove duplicates' function and checked with manual screening. Remaining articles were then uploaded to Covidence [22] for screening. Two researchers (MM and AS) independently reviewed title and abstracts, and irrelevant papers were excluded. The same reviewers then assessed the full text of each paper for relevance and eligibility. Conflicts that arose were

discussed and dealt with via consensus and irrelevant papers were excluded. Reference lists of the final included studies were pearled for any extra papers that may have been missed in the systematic searches. All relevant data were extracted to an Excel spreadsheet created by the primary researcher (MM) and checked for errors by another researcher (AS). Again, discrepancies were resolved via consensus.

Risk of bias in individual studies was assessed using the McMaster critical appraisal tool for quantitative studies. This was completed by primary researcher MM and checked by AS. Studies were appraised based on 13 criteria in the categories of study purpose, literature, design (Randomised Controlled Trial (RCT), Controlled Trial (CT) or other), sample, outcomes, intervention, results, and conclusions and clinical implications. For each of the 13 criteria, one point was awarded for a 'yes' or 'addressed' answer, and no points were awarded for 'no' or 'not addressed'; RCTs were awarded two points, CTs were awarded one point, and other designs were awarded no points.

Results

The initial searches in April 2018 returned 470 references, 118 of which were removed during duplicate screening. The title and abstract screening of the remaining 352 studies resulted in 14 full text studies meeting inclusion. Eight of these studies were subsequently excluded at the full text phase due to including wrong intervention (modality of exercise), wrong study design, duplicates missed during the initial phase or conference abstracts (Figure 1). Six studies met final inclusion; of these, two studies incorporated data from two separate experiments, resulting in eight experiments available for narrative synthesis. A second search was then conducted in May 2019. This search returned 153 references, 44 of which were removed during duplicate screening. Following title and abstract screening of the remaining 109 papers, and subsequent full text screening of 5 papers, 2 full text studies met final inclusion (Figure 1).

Four types of non-invasive brain stimulation neuroplasticity paradigms were identified in the final included studies (Table 1); Six studies induced neuroplasticity with LTP-like neuroplasticity

paradigms including PAS (three studies), iTBS (two studies) or anodal tDCS (one study). Two other studies induced neuroplasticity with an LTD-like paradigm using cTBS or cathodal tDCS. Duration of the paradigms ranged from 40 seconds (cTBS) to 30 minutes (PAS).

A total of 128 participants were included in the narrative synthesis. Approximately 65% of participants were female, and the average age of participants was 29.6 years. High levels of physical activity or fitness were indicated as exclusion criteria in two studies [23, 24]. In these studies, individuals engaging in more than or equal to 3000 metabolic equivalents in the seven days preceding participation were excluded. This was based on individual self-reported physical activity using the International Physical Activity questionnaire (IPAQ).

Four types of neuroplasticity paradigms were used, including PAS, cTBS, iTBS and tDCS (Table 1). Six of the eight included studies applied the neuroplasticity paradigm immediately following completion of exercise [23-28]. Two studies delivered the neuroplasticity paradigm before exercise [29, 30] (see Appendix A for detailed summary of study design). The included studies measured responses to neuroplasticity paradigms as changes in the amplitudes of MEPs in intrinsic hand muscles. Two of the eight studies measured MEP amplitude only once following the neuroplasticity paradigm (approximately two to three minutes after completion of PAS) [26, 27], with the remaining six studies assessing potential changes in MEP amplitude at multiple time points (ranging from immediately post-paradigm to 90 minutes post-paradigm).

All exercise paradigms were performed on a stationary exercise bike or treadmill. Three studies [26-28] utilized a high intensity interval exercise paradigm, where all participants were required to cycle for intermittent bouts of low and high intensities. Two studies [25, 29] required participants to cycle for 20 minutes at 65-75% predicted maximum heart rate, whereas one study [23] required participants to cycle at 80% predicted maximum heart rate for 30 minutes. Three studies utilized a repeated measures design, where participants were required to attend multiple sessions in which they cycled at a low or moderate intensity[24], performed treadmill exercise at a low or high intensity[30], performed high-intensity interval cycling or moderate intensity continuous cycling[28], or performed seated rest. Throughout the interventions all studies measured either rate of perceived exertion (RPE) [31], or

rotations per minute (RPM). All included studies required participants to perform a bout of seated rest as the control condition. See Appendix A for a full description of exercise paradigms.

The included studies scored between 7 and 10 for the McMaster critical appraisal tool (Table 2). All studies were classified as crossover Controlled Trials, although two studies did not explicitly specify the randomisation of participants to conditions or pseudo-randomisation of condition order [26, 27]. No included studies justified their sample sizes, however all specified inclusion criteria. Two studies reported participant dropouts, and the remaining six did not specify. No study reported reliability or validity statistics for their outcome measures.

Discussion

This review identified eight papers, containing a total of twelve experiments, that have investigated the effect of acute aerobic exercise on non-invasive brain stimulation measures of neuroplasticity. Eight experiments utilized paradigms that aimed to induce LTP-like neuroplasticity [23, 25-28, 30], and four utilized paradigms to induce LTD-like neuroplasticity [24, 29, 30]. Of the 12 experiments (Appendix A), seven reported neuroplastic changes in the expected direction [24-29]. These experiments required participants to cycle for either 20 minutes of 'high intensity' intervals, 25 minutes of 'moderate intensity' continuous or 30 minutes of 'low intensity' continuous sessions. Conversely, five experiments reported no effect (or unexpected effects) of exercise on plasticity induction [23, 24, 29, 30]. Briefly, these experiments required participants to undertake a bout of continuous cycling or treadmill exercise, with exercise prescription ranging from 30 minutes of low intensity walking to 30 minutes of high intensity continuous cycling.

Although it is well accepted that engaging in aerobic exercise holds important benefits for brain health, the optimal type, intensity and duration of exercise to maximise brain health benefits remains unknown. In this review, the greatest changes in neuroplasticity were observed in experiments that either applied a high intensity interval cycling paradigm, in which participants were asked to cycle for intermittent bouts of high (90% predicted HRR) and low (50% predicted HRR) intensities for a total

of twenty minutes[26-28], or in experiments that applied a longer, continuous bout of moderate intensity continuous cycling[24]. Andrews et al.[28] argued that high-intensity interval training induced greater neuroplastic changes following iTBS than a bout of moderate intensity continuous cycling for 20 minutes at 50% predicted HRR. These findings align with those of Smith et al.[23], who similarly observed no facilitation of MEP amplitude following continuous exercise of 30 minutes at 80% predicted HRR and iTBS. Interestingly, McDonnell et al.[24] reported an enhanced neuroplastic response when low intensity continuous exercise preceded cTBS, but not moderate-intensity continuous exercise. It is plausible that the differences between high intensity interval training and lower-intensity continuous training, compared to continuous exercise at higher intensities, are a function of differences in acute physiological effects. Higher exercise intensities have been previously shown to elevate cortisol levels, acutely [32]. In addition, elevated cortisol has been reported to block the effects of non-invasive brain stimulation neuroplasticity paradigms in humans [33]. Similarly, animal studies have shown that a single bout of high intensity continuous aerobic exercise fails to influence plasticity-related protein expression in the rat sensorimotor cortex [34]. Thus on balance, it is possible that elevated cortisol levels resulting from the high intensity continuous exercise blocked the effects of the neuroplasticity paradigms. An additional factor that may contribute to the differences between interval and continuous exercise is the regulation of brain glycogen levels which are depleted considerably following longer bouts of moderate to high intensity exercise [35]. It may be plausible that the presence of recovery periods spaced amongst the high intensity intervals allowed for cortisol and/or glycogen levels to be maintained at a level that did not block the neuroplasticity response of the motor cortex, although this is somewhat speculative because neither cortisol or glycogen levels were assessed in any of these studies.

A noteworthy finding of the current review is that those experiments that applied the neuroplasticity paradigm (tDCS or cTBS) *before* undertaking a bout of aerobic exercise did not observe significant or expected changes in MEP amplitude[29, 30], whereas those that used aerobic exercise as a 'primer' for the neuroplasticity paradigms more frequently reported the expected changes. Whilst McDonnell et al.[24] reported maximum facilitation of LTP-like neuroplasticity when aerobic exercise preceded cTBS,

253 other studies that performed exercise after either cTBS [29] or anodal or cathodal tDCS[30] showed
254 completely abolished effects. Previous research has demonstrated that cTBS is more effective in
255 inducing LTD-like effects in the absence of prior voluntary motor cortex (M1) activity[36], and
256 voluntary M1 activity following cTBS has been shown to completely reverse inhibitory effects[37].
257 These homeostatic mechanisms have been summarized conceptually in both humans[38] and animals[39,
258 40] as the Bienenstock- Cooper- Munro (BCM) theory, whereby increased periods of postsynaptic
259 activity subsequently raises the threshold for inducing neuroplasticity[41]. Taken together, these
260 findings outline the importance of the timing of exercise in relation to the application of the
261 neuroplasticity paradigm, such that aerobic exercise is likely more effective when used as a 'primer'.

262 Given the magnitude of changes in neuroplasticity reported by multiple studies in this review, the
263 eventual use of TMS paradigms in conjunction with aerobic exercise to promote motor cortical
264 neuroplasticity appears feasible. However, as is the case in brain stimulation research more broadly,
265 there are substantial limitations to be considered. All participants included in this review were young,
266 healthy and able to tolerate exercise well, therefore these findings are not yet generalizable to clinical
267 populations or older adults. Indeed, previous research has demonstrated that aerobic exercise does not
268 facilitate the response to TMS neuroplasticity paradigms in stroke patients[42], and thus any
269 generalisations to clinical populations derived from the experiments in this review must be made with
270 caution. Based on the current literature there is limited scope to identify an optimal experimental
271 design for facilitating neuroplasticity with aerobic exercise. This is largely due to a number of factors
272 including small sample sizes, lack of control conditions (comparing a bout of high intensity exercise
273 to a bout of low intensity continuous exercise with no rest condition, for example), limited study
274 replication and inconsistency in reporting of results. Future research should aim to replicate
275 previously published experiments with larger sample sizes and broader participant ages to strengthen
276 previous findings, and inform a more standardized approach to brain stimulation and aerobic exercise
277 research moving forwards.

278 **Conclusion**

This review summarized the current literature investigating whether acute aerobic exercise enhances the response to experimentally-induced TMS neuroplasticity paradigms in the human motor cortex. The number of studies in this field to date are minor, but current results suggest that aerobic exercise interventions may be more effective when used as a 'primer' for induction of neuroplasticity via brain stimulation, rather than following the neuroplasticity paradigm. Furthermore, shorter bouts of low-intensity interval exercise or longer bouts of continuous exercise at lower intensities may be more effective for neuroplasticity induction than longer bouts of higher intensity continuous exercise. It is speculated that this may be a function of cortisol and glycogen levels resulting from the different intensities of aerobic exercise. Future research is encouraged to replicate current studies in broader age groups and with larger sample sizes to inform a more standardized approach to exercise and neuroplasticity research, and to better understand this relationship.

Practical Implications

- Acute aerobic exercise has the capacity to enhance the response to experimentally-induced brain stimulation neuroplasticity paradigms
- Shorter bouts of high-intensity interval exercise or longer bouts of lower-intensity continuous exercise may be more effective in inducing neuroplasticity than continuous bouts of exercise at higher intensities
- Aerobic exercise interventions may be more effective in neuroplasticity induction when used as a primer rather than following the brain stimulation paradigm

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425

426

427

428 **Table 1**

Neuroplasticity Paradigm	Description	Type of neuroplasticity induced	*n* studies
Paired Associative Stimulation (PAS)	Combines TMS over contralateral motor cortex with low-frequency electrical stimulation of a peripheral nerve [43].	Increase in MEP amplitude LTP-like	3
Continuous Theta-Burst Stimulation (cTBS)	Uses TMS to deliver uninterrupted bursts of 3 stimuli to cortical areas at 50Hz, repeated at 5 Hz for 40 seconds (600 stimuli). Applied using low intensity (80% AMT) [15].	Decrease in MEP amplitude LTD-like	2

Intermittent Theta-Burst Stimulation (iTBS)	Uses TMS to deliver bursts of 3 stimuli at 50 Hz, repeated at 5 Hz for 2 seconds every 10 seconds (600 stimuli). Applied using low intensity [15].	Increase in MEP amplitude LTP-like	2
Transcranial Direct Current Stimulation (tDCS)	Uses a direct current stimulator to deliver a weak electrical current (0.5-2mA) between two electrodes (anode and cathode). Electrode montage may be cephalic, extracephalic or a combination. Stimulation may be 'anodal' (excitatory) or 'cathodal' (inhibitory). [44]	Increase *or* decrease in MEP amplitude LTP- and LTD-like	1

429 TMS = transcranial magnetic stimulation; LTP = long-term potentiation; LTD = long-term

430 depression; AMT = active motor threshold; MEP = motor evoked potential

Table 2

		Mang, Brown et al. (2016) [27]	Baltar et al. (2018) [30]	Andrews et al. (2019) [28]	Mang, Snow et al. (2014) [26]	Singh, Neva & Staines (2014) [25]	Smith et al. (2018) [23]	McDonnell et al. (2013) [24]	Singh, Duncan & Staines (2016) [29]
STUDY PURPOSE	Was the purpose stated clearly?	✓	✓	✓	✓	✓	✓	✓	✓
LITERATURE	Was relevant background literature reviewed?	✓	×	✓	✓	✓	✓	✓	✓
DESIGN	Randomized Controlled Trial (RCT) or Controlled Trial (CT)?	CT	CT	CT	CT	CT	CT	CT	CT
SAMPLE	Was the sample	✓	✓	✓	✓	✓	✓	✓	✓

	described in detail?								
	Was sample size justified?	×	×	×	×	×	×	×	×
OUTCOMES	Were the outcome measures reliable?	×	×	×	×	×	×	×	×
	Were the outcome measures valid?	×	×	×	×	×	×	×	×
INTERVENTION	Intervention was described in detail?	✓	✓	✓	✓	✓	✓	✓	✓
RESULTS	Results were reported in terms of statistical significance?	✓	✓	✓	✓	✓	✓	✓	✓

	Were the analysis method(s) appropriate?	✓	×	✓	✓	✓	✓	✓	✓
	Clinical importance was reported?	✓	✓	✓	✓	✓	✓	✓	✓
	Drop-outs were reported?	✓	×	×	×	✓	×	×	×
CONCLUSIONS AND CLINICAL IMPLICATIONS	Conclusions were appropriate given study methods and results?	✓	✓	✓	✓	✓	✓	✓	✓
	TOTAL SCORE/14	10	7	9	9	10	9	9	9

Note. The McMaster Critical Appraisal Tool used to evaluate quality of included papers. Ticks represent one point awarded, crosses represent no points awarded.

Figure legends:

Figure 1: PRISMA flow diagram describing screening processes.